

REMARKS

Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-82 are pending. Claims 1-3, 6, 7, 11-13, 15, 23, 24, 27-30, 49, 53, 60, and 75-77 have been amended. Claims 4, 5, 14, 17, 26, 36, 39-42, 44, 54-59, 61, and 62 are original. Claims 9, 19, 21, 22, 25, 34, 38, 43, and 50-52 have been previously presented. Claims 78-82 are new. Claims 8, 10, 16, 18, 20, 31-33, 35, 37, 45-48, and 63-74 have been canceled. No new matter has been introduced by the amendment.

1. Claim Objection

Claim 76 has been objected to under 37 CFR 1.75(c), as being improper dependent form. The Examiner asserts that simultaneous introduction of three-plug fluids is “an inherent feature of the method of the parent claims”, “since without such simultaneous introduction no plug, which contain all three fluids recited in claims 1 and 3, could be formed” (Office Action, page 2). The Applicants respectfully disagree. The plugs can be formed either by simultaneous introduction of the plug-fluids (claim 76) or by forming a plurality of drops from the plug-fluids, where the plurality of plugs is formed when at least two of the drops merge in the first microchannel (claim 77). Thus, claim 76 further limits the subject matter of its previous claim. Accordingly, the Applicants respectfully submit that the objection to claim 76 is improper and should be withdrawn.

2. Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 have been rejected under 35 U.S.C. § 112, first paragraph, regarding using microchannel and having a particular capillary number. Claims 1-2, 4-7, 23, 26, 36, 38-40, 49-62, and 75-77 have been rejected under 35 U.S.C. § 112, first paragraph, regarding applying pressure. The Applicants respectfully traverse these rejections based on the following remarks.

Claims 1 and 2 have been amended to read “pressure is applied when introducing each of the first, second and third plug-fluids, and at least one of the first, second, and third plug-fluids forms an interface with the first carrier fluid after the plug-fluids contact the first carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the first microchannel in the first carrier-fluid, at least one of the plugs comprising the first, second and third plug-fluids” and “pressure is applied when introducing each of the fourth, fifth and sixth plug-fluids, and at least one of the fourth, fifth and sixth plug-fluids forms an interface with the second carrier fluid after the plug-fluids contact the second carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the second microchannel in the second carrier-fluid, at least one of the plugs comprising the fourth, fifth and sixth plug-fluids”, respectively. The term “channel” has been replaced with “microchannel”. Support for amended claims 1 and 2 can be found in Applicants’ specification, for example, in original claims 1 and 2; and in page 29, lines 10-29.

Accordingly, the Applicants respectfully submit that the 35 U.S.C. § 112, first paragraph rejections have been overcome and should be withdrawn.

3. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

A. Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77

Claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicants respectfully traverse these rejections based on the following remarks.

The term “plug-fluid” is defined in the specification in page 15, lines 27-34. Accordingly, the Applicants respectfully submit that the term “plug-fluids” is clear.

Regarding whether the plug-fluids are introduced continuously or discontinuously into the microchannels, both ways are contemplated and within the scope of the claims. Plugs are formed, for example, where at least one of the first, second, and third plug-

fluids forms an interface with the first carrier fluid after the plug-fluids contact the first carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the first microchannel in the first carrier-fluid, as required in claim 1.

Claim 3 has been amended to read “where the one or more first plug-fluids comprise a precipitant and a crystallization target; and where at least one plug of the first plug type comprises the precipitant and the crystallization target”, “a second plug-forming region of the first microchannel”, “a second plug-forming region of a second microchannel”, and “where the one or more second plug-fluids comprise a precipitant; where at least one of the plugs of the second plug type comprises the precipitant”.

Claims 6 and 7 have been amended to be in a proper antecedent form.

Regarding claims 6, 38, 40, and 44, as argued in our response dated September 19, 2008, “permeable” is commonly understood to mean “capable of being permeated; penetrable.” Merriam-Webster’s Collegiate Dictionary (11th ed.). “Permeable” and “permeability” can be used in connection with a liquid-liquid relationship. The term “immiscible” is defined in the specification as “the resistance to mixing of at least two phases or fluids under a given condition or set of conditions (e.g., temperature and/or pressure) such that the at least two phases or fluids persist or remain *at least partially separated* even after the phases have undergone some type of mechanical or physical agitation. Phases or fluids that are immiscible are typically physically and/or chemically discernible, or they may be separated *at least to a certain extent*.” (page 13, lines 26-31; emphasis added). Accordingly, the Applicants respectfully submit that the carrier fluid can be both immiscible with and permeable to water.

Regarding claim 25, the meaning of the term “indexing marker” is clear. The indexing marker can be any suitable substance. Claim 25 depend from claim 24. The indexing marker as recited in claim 25 is such that “where one or more of the respective flow rates are varied so that the concentration of [the indexing marker] in at least one of the plugs of one plug-type provides a correlative and quantitative measure of a second component in an adjacent plug.”

Claims 27-30 have been amended to replace “osmolality” with “salt concentration”. Accordingly, the Applicants respectfully submit that the meaning of claims 27-30 is clear. Support for amended claims 27-30 can be found in Applicants’ specification, for example, in page 88, lines 14-15.

Claim 49 has been amended to read “where at least one plug-fluid comprises a marker so that the presence of the marker in a plug comprising the at least one plug-fluid provides a correlative and quantitative measure of a component in an adjacent plug.” Accordingly, the Applicants respectfully submit that the meaning of claim 49 is clear. Support for amended claim 25 can be found in the Applicants’ specification, for example, in original claim 24.

Regarding claims 52 and 57, the Applicants’ specification discloses how a capillary tube is used in the method (page 88, line 5 to page 89, line 11; and Fig. 46). Accordingly, the Applicants respectfully submit that the meaning of claims 52 and 57 is clear.

Claims 53-59 recite where the crystal is removed or collected, which is relevant to the subject matter of the parent claim (a method of crystallization).

Claim 60 has been amended to read “where water evaporates from the plugs.” Accordingly, the Applicants respectfully submit that the meaning of claim 60 is clear.

Claim 75 has been amended to be in a proper antecedent form.

Regarding claim 77, the Applicants’ specification discloses how two plugs can be merged (page 40, line 32 to page 42, line 12). Accordingly, the Applicants respectfully submit that the meaning of claim 77 is clear.

In view of the above amendments and remarks, the Applicants respectfully submit that claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 particularly point out and distinctly claim the subject matter which applicant regards as the invention. Accordingly, the rejections against claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 should be withdrawn.

B. Claims 1-9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77

Claims 1-9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 have been rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. The Applicants respectfully traverse these rejections based on the following remarks.

The plug fluids do not have to be mixed first in order to form plugs. For example, the plug fluids can be either introduced simultaneously or non-simultaneously (see the discussion in section 1 above). In another example, the plug fluids can “initially coflow preferably along a short or minimal distance before coming in contact with the carrier-fluid” and forming plugs (page 27, lines 11-21). Accordingly, the Applicants respectfully submit that the rejections against claims 1-9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 are improper and should be withdrawn.

4. Claim Rejections under 35 U.S.C. § 103

Claims 1-7, 9, 11-15, 17, 19, 21-22, 24-30, 34, 36, 38-44, 51-62, and 75-77 have been rejected under 35 U.S.C. § 103(a) over Weigl et al. (U.S. Pat. No. 6,409,832) in view of Chayen (J. Cryst. Growth, 1999). Claim 23 has been rejected under 35 U.S.C. § 103(a) over Weigl in view of Chayen, and further in view of Bardell et al. (U.S. Pat. Pub. No. 2001/0048900 A1). Claims 49 and 50 have been rejected under 35 U.S.C. § 103(a) over Weigl in view of Chayen, and further in view of Pantoliano et al. (U.S. Pat. No. 6,569,631). The Applicants respectfully traverse these rejections based on the following remarks.

Weigl discloses a microfluidic system where the fluids either form a laminar flow (see Fig. 1; and column 11, line 54 to column 12, line 8) or form a homogeneous solution (see Fig. 2; and column 12, lines 9-19). When a laminar flow is formed, the two fluids do not mix other than by mutual self-diffusion (see column 12, lines 52-54). When a homogeneous solution is formed, the homogeneous solution is transported to the entire microfluidic channel (39) for crystallization (see column 14, lines 21-24; and Fig. 8). As noted by the Examiner, Weigl does not disclose crystallization in plugs formed by the plug-fluids (Office Action, page 7).

The Examiner asserts that “while Weigl teaches a homogeneous mixing in the laminar flow, it is not apparent, as to what may prevent such homogeneous mixing in the plugs (or droplets) which seems to be inherent for the small volumes of liquids” (Office Action, page 9). Weigl, however, teaches that *both* the laminar flow *and* the homogenous solution designs are essential for the crystallization methods (“This action [laminar flow] establishes a concentration gradient in device 10, which allows for a very well defined crystallization. Solvent molecules from one stream can diffuse into a parallel stream containing a different solvent and particles. The change in solvent properties along diffusion interface zones 16, 18 can then induce crystallization or precipitation.” See column 11, line 64 to column 12, line 3; column 15, lines 36-43. “The protein sample and the reagent are mixed at a certain ratio, and then flow into crystallization channel 15, where a homogeneously mixed solution 22 is slowed or stopped. Crystallization will then occur inside channel 15.” See column 12, lines 14-18.) The Applicants thus respectfully submit that the Examiner’s proposed modification to Weigl by introducing plugs to the Weigl design would prevent the formation of either a laminar flow or a homogeneous solution, thus defeat the purpose of the Weigl disclosure. In other words, Weigl teaches away from the Examiner’s proposed modification to Weigl by introducing plugs to the Weigl design as disclosed in Chayen.

Also, Weigl teaches a high density screening crystallization cartridge 50 (see Fig. 11 and column 14, line 59 to column 15, line 19). The screening is carried out by forming a series of microfluidic channels connected to their respective, separate solution reservoir (see Fig. 11). Weigl does not teach or suggest adjusting the screening conditions by varying flow rate of the fluids in the same microfluidic channel.

Further, although having conceded that Weigl does not disclose crystallization in plugs formed by the plug-fluids (Office Action, page 7), the Examiner nevertheless attempted to cure this deficiency of Weigl by asserting that Chayen teaches “preferences of microbatch crystallization in *droplets suspended in oil*, which are similar to plugs separated by an immiscible carrier fluid in microfluidic channels” (Office Action, page 7; emphasis added). Chayen, however, explicitly teaches that in microbatch experiments,

“crystals are grown in 1-2 μ L drops of a mixture of protein and crystallising agents” (page 434, right column; page 437, right column to page 438, left column; and Fig. 2). The Applicants respectfully submit that the Examiner fails to establish any reason why *droplets suspended in oil* used in a microbatch experiment as disclosed by Chayen would be similar to *plugs formed by plug-fluids in a microfluidic system*.

Also, neither Weigl nor Chayen teaches or suggests “at least one of the first, second, and third plug-fluids forms an interface with the first carrier fluid after the plug-fluids contact the first carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the first microchannel in the first carrier-fluid”, as required by amended independent claim 1.

In view of the above amendments and remarks, the Applicants respectfully submit that Weigl in view of Chayen do not teach or suggest all the claim limitations as recited in claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77. Accordingly, the rejections against claims 1-7, 9, 11-15, 17, 19, 21-30, 34, 36, 38-44, 49-62, and 75-77 are improper and should be withdrawn.

5. New Claims

New claims 78 and 79 depend from amended independent claim 1, and thus should be allowable as well. Support for new claim 78 and 79 can be found in Applicants' specification, for example, in page 29, lines 10-29.

New independent claim 80 recites introducing into a first inlet in fluid communication with the first microchannel a first plug-fluid comprising a precipitant; and a second plug-fluid comprising a crystallization target, and where pressure is applied when introducing each of the first and second plug-fluids, and at least one of the first and second plug-fluids forms an interface with the first carrier fluid after the plug-fluids contact the first carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the first microchannel in the first carrier-fluid, at least one of the plugs comprising the first and second plug-fluids. New independent

claim 82 recites introducing into a first inlet in fluid communication with the first microchannel a first plug-fluid comprising a first reagent; and a second plug-fluid comprising a second reagent, and where pressure is applied when introducing each of the first and second plug-fluids, and at least one of the first and second plug-fluids forms an interface with the first carrier fluid after the plug-fluids contact the first carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the first microchannel in the first carrier-fluid, at least one of the plugs comprising the first and second plug-fluids. Support for new claim 80-82 can be found in Applicants' specification, for example, in page 29, lines 10-29; page 28, lines 18-21; and in page 27, lines 18-21.

As discussed in section 4 above, these new claims should be allowable over the cited references.

6. Conclusion

Based on the above amendments and remarks, the Applicants respectfully submit that the claims are in condition for allowance. The Examiner is kindly invited to contact the undersigned agent to expedite allowance.

Respectfully submitted,

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